This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

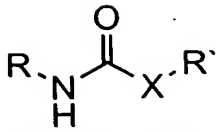
Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

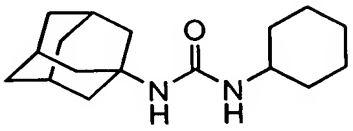
As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

Figure 1

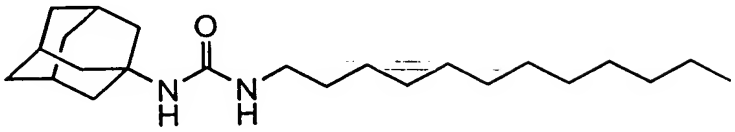


X: NH, O, or CH_2

R and R`: alkyl or aryl groups



192



686

Figure 2

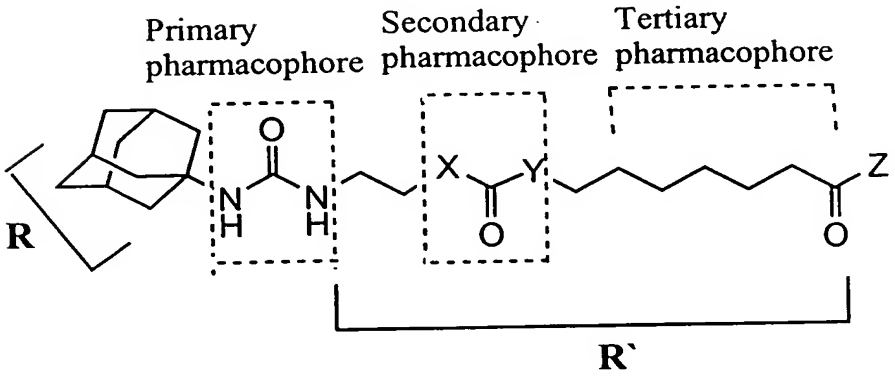


Figure 3

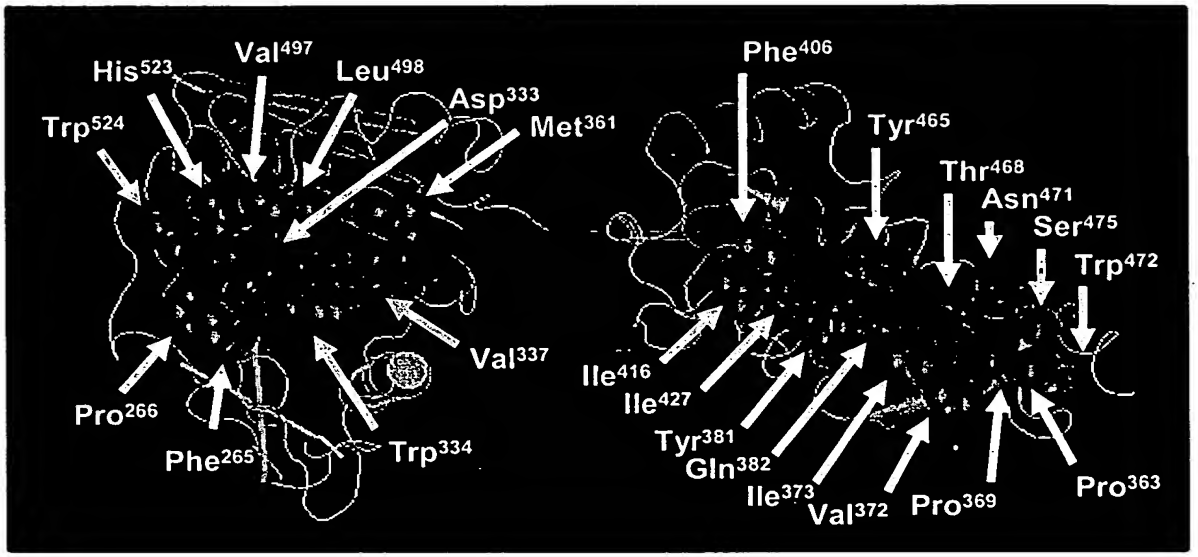
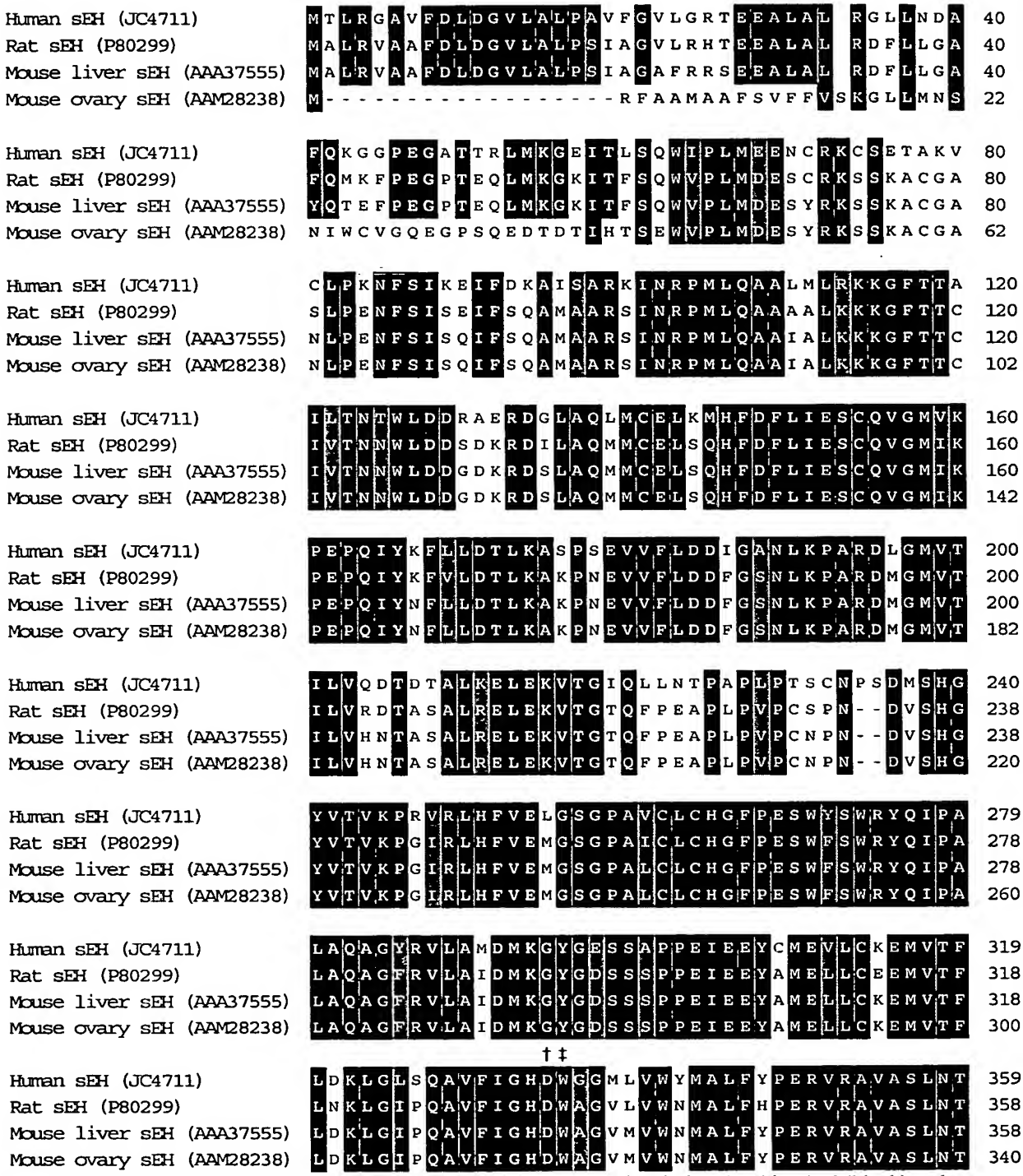
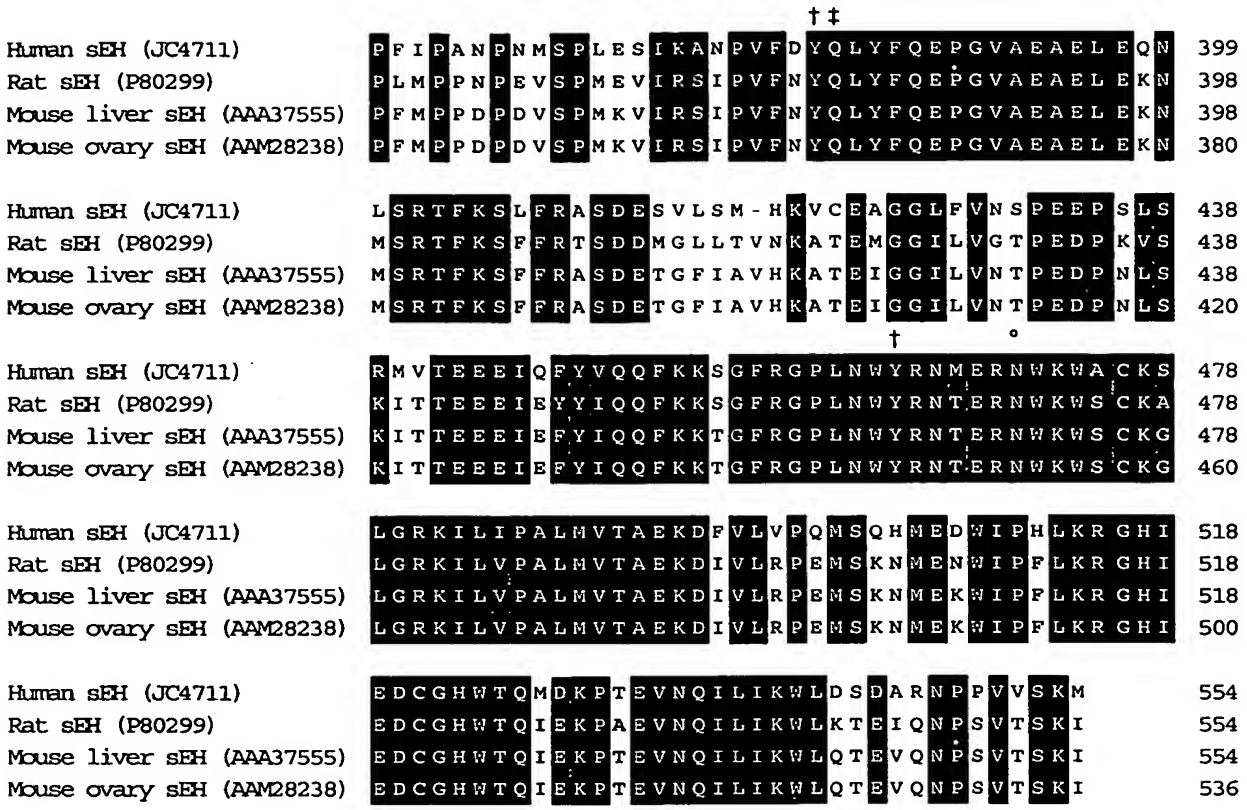

His523
Val497
Leu498
Asp333
Met361
Trp524
Val337
Pro266
Phe265
Trp334
Phe406
Tyr465
Thr468
Asn471
Ser475
Trp472
Ile416
Ile427
Tyr381
Gln382
Ile373
Val372
Pro369
Pro363

Figure 4



Protein sequences obtained from the NCBI database (accession numbers) showing identical (black) and homologous (gray) residues in the mammalian proteins. Sites for primary (†), secondary (‡) and tertiary (°) pharmacophores are indicated above each sequence.

Figure 5



Protein sequences obtained from the NCBI database (accession numbers) showing identical (black) and homologous (gray) residues in the mammalian proteins. Sites for primary (†), secondary (‡) and tertiary (°) pharmacophores are indicated above each sequence.

Figure 6

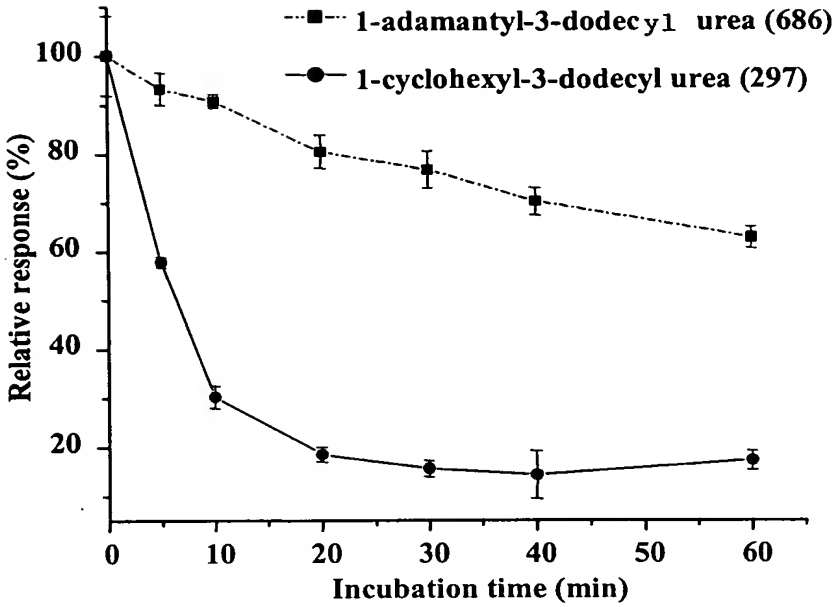


Figure 7

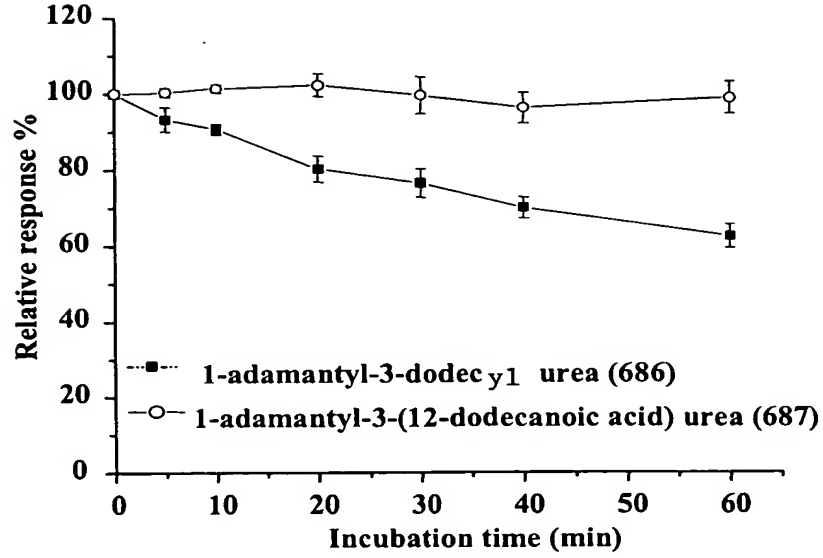


Figure 8

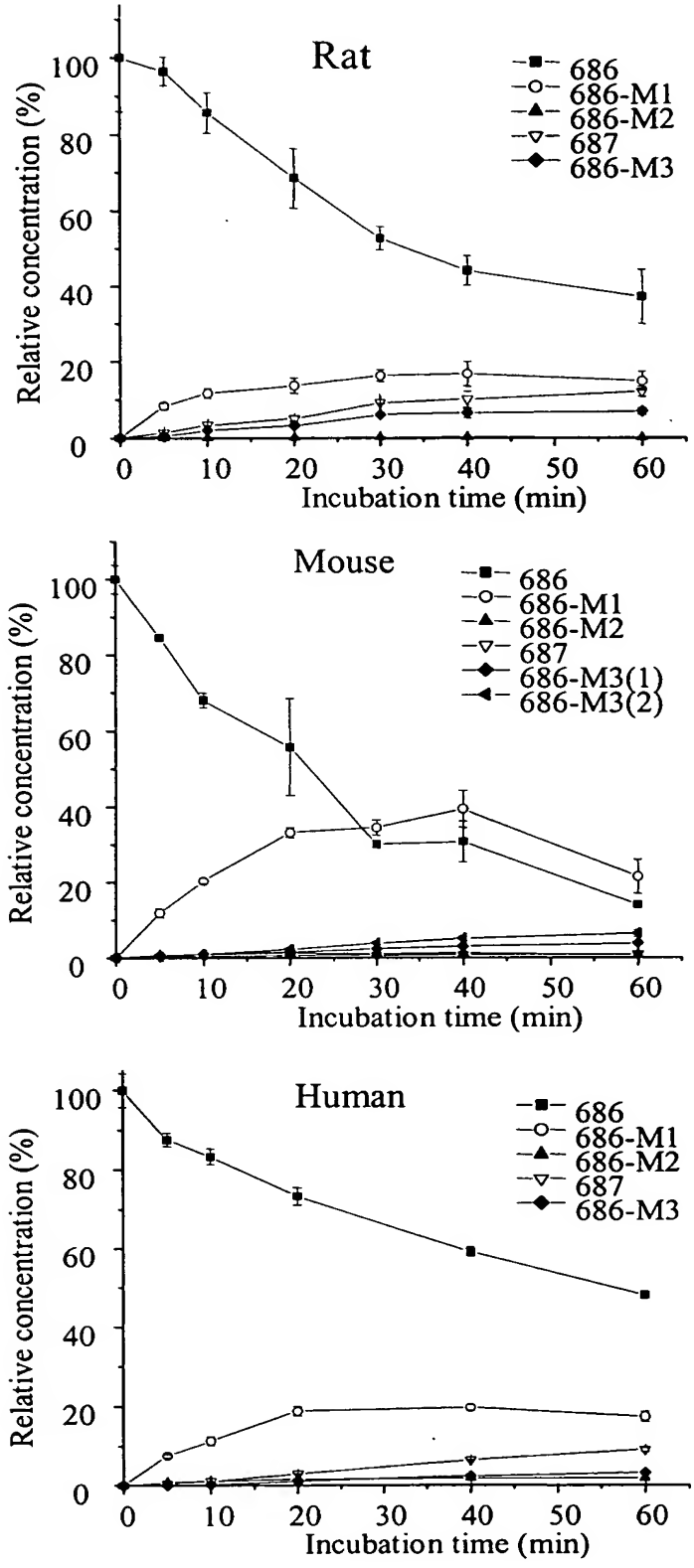

Rat
686
686-M1
686-M2
687
686-M3
Relative concentration (%)
Incubation time (min)
Mouse
686
686-M1
686-M2
687
686-M3(1)
686-M3(2)
Relative concentration (%)
Incubation time (min)
Human
686
686-M1
686-M2
687
686-M3
Relative concentration (%)
Incubation time (min)

Figure 9

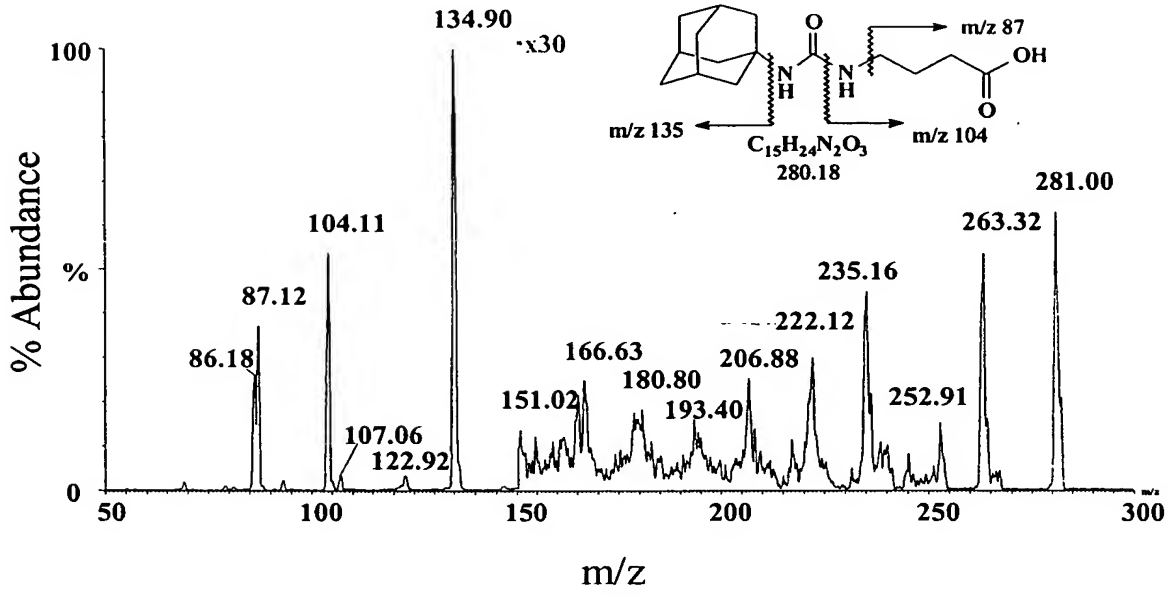


Figure 10

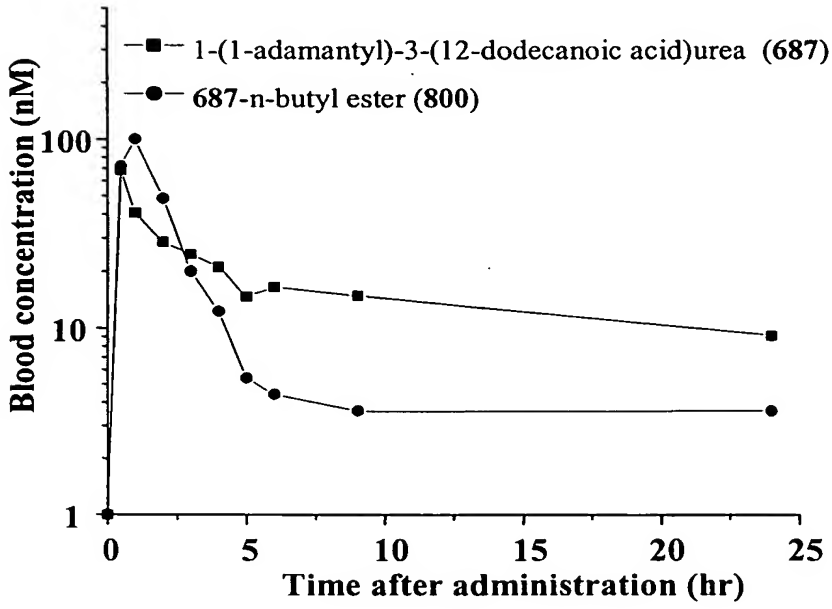


Figure 11

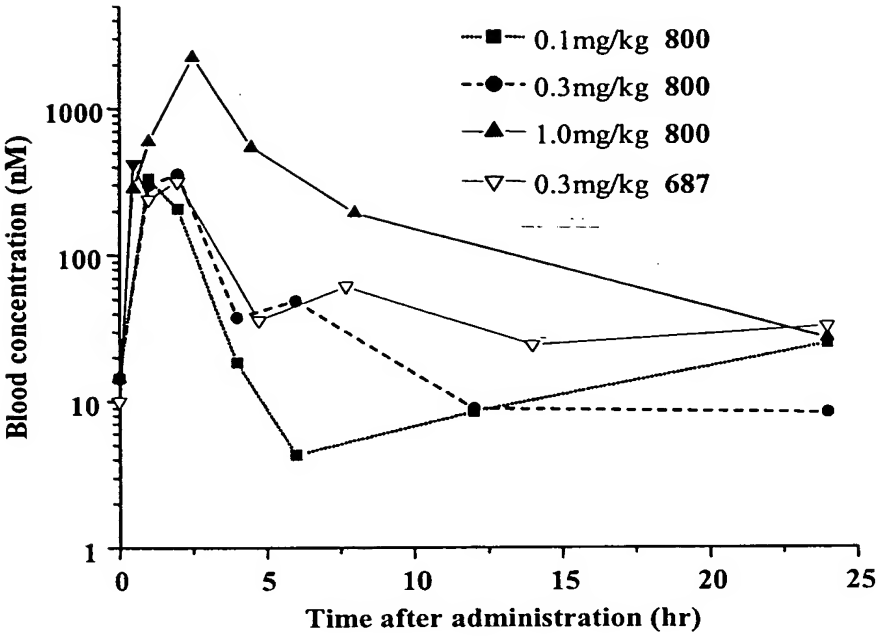

0.1mg/kg 800
0.3mg/kg 800
1.0mg/kg 800
0.3mg/kg 687
Blood concentration (nM)
1000
100
10
1
0
5
10
15
20
25
Time after administration (hr)

Figure 12

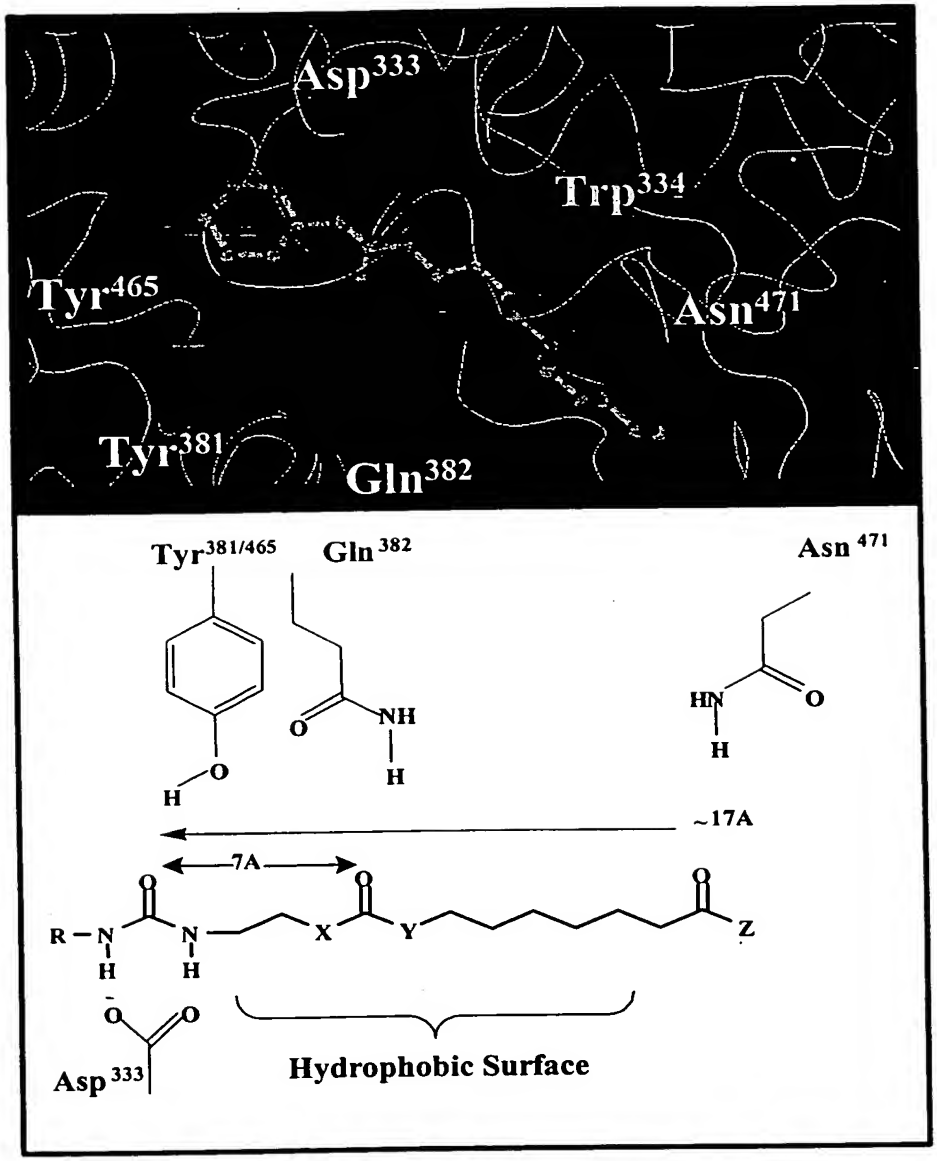
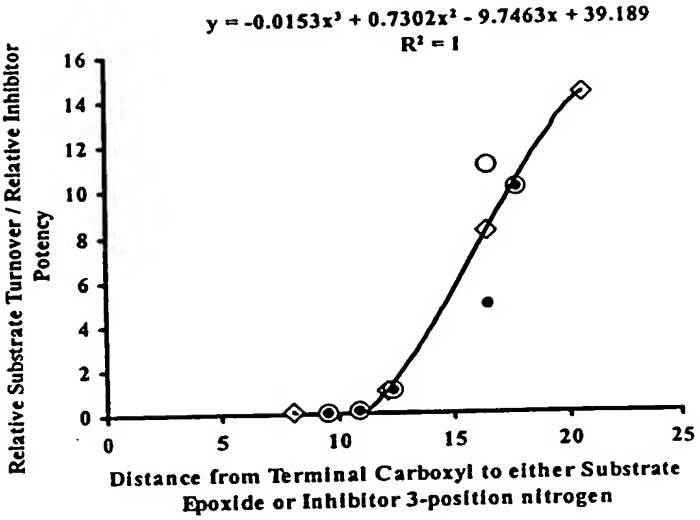

Asp333
Trp334
Tyr465
Asn471
Tyr381
Gln382
Tyr381/465
Gln 382
Asn 471
~17A
7A
R
N
H
X
Y
Z
Asp 333
Hydrophobic Surface

Figure 13

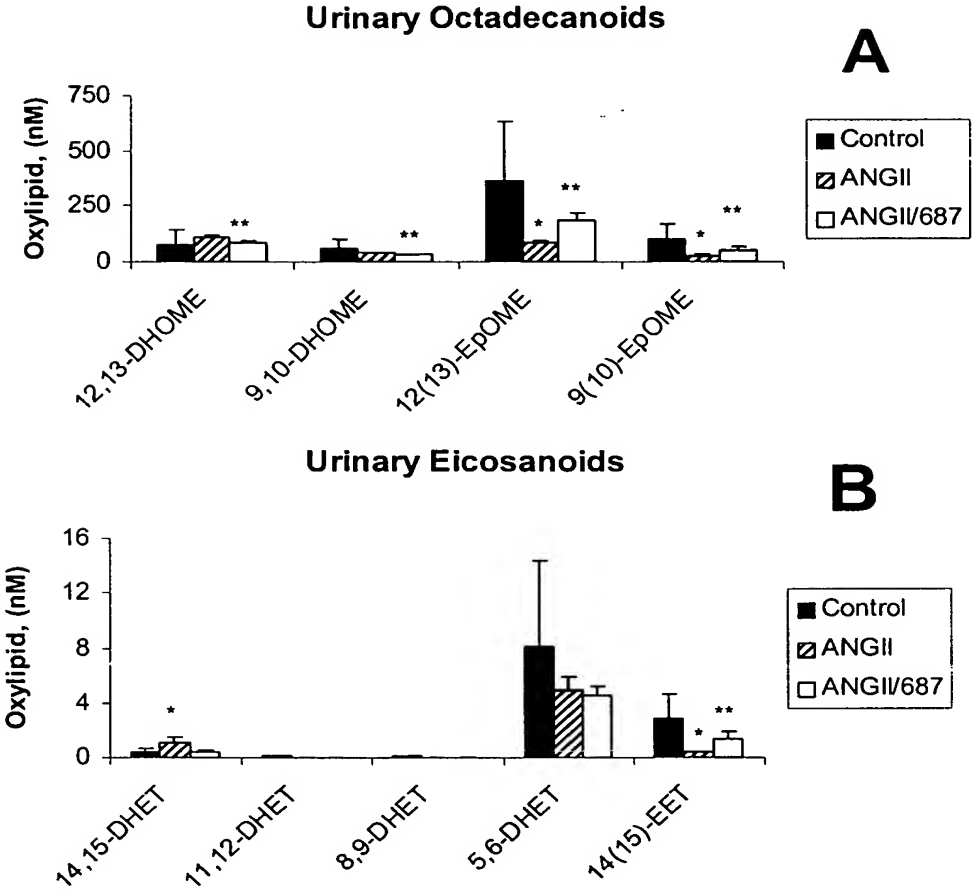


◇ Relative EET Turnover

○ Inhibitor Rank-order potency with MsEH

● Inhibitor Rank-order potency with HsEH

Figure 14


Urinary Octadecanoids
A
Oxylipid, (nM)
750
500
250
0
Control
ANGII
ANGII/687
12,13-DHOME
9,10-DHOME
12(13)-EpOME
9(10)-EpOME
Urinary Eicosanoids
B
Oxylipid, (nM)
16
12
8
4
0
Control
ANGII
ANGII/687
14,15-DHET
11,12-DHET
8,9-DHET
5,6-DHET
14(15)-EET